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EXAMINER	
SPIEGLER, ALEXANDER H	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,741	HERMAN ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *1-7 and 13-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/7/03, 4/28/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. After further consideration, a new restriction requirement has been set forth below.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

1. Claims 1-7 (in part), drawn to methods of screening or identifying a subject at risk of developing Vascular Response using 2D electrophoresis, classified in class 204, subclass 456, for example.
2. Claims 1-7 (in part), drawn to methods of monitoring the effects of therapy administered in a subject using 2D electrophoresis, classified in class 204, subclass 461, for example.
3. Claims 8-12 (in part), drawn to methods of screening or identifying a subject at risk of developing Vascular Response using proteins, classified in class 435, subclass 7.1, for example.
4. Claims 8-12 (in part), drawn to methods of monitoring the effects of therapy administered in a subject using proteins, classified in class 514, subclass 1, for example.
5. Claims 13-16, drawn to proteins and kits comprising said proteins, classified in class 530, subclass 350, for example.
6. Claims 17-23, drawn to antibodies and kits comprising said antibodies, classified in class 530, subclass 387.1, for example.
7. Claim 24, drawn to methods of treating Vascular Response using a protein, classified in class 514, subclass 2, for example.

8. Claim 25, drawn to methods of treating Vascular Response using an antibody, classified in class 424, subclass 130.1, for example.

9. Claims 26-28, drawn to drawn to methods of treating Vascular Response using a nucleic acid, classified in class 514, subclass 44, for example.

10. Claims 29-31, 43 and 45-46, drawn to methods of screening for agents that interact with a polypeptide, classification undeterminable; classification dependent on agent.

11. Claims 32-42, 44-46, 50 and 55, drawn to methods of screening agents that modulate expression or activity of a VRPI, classification undeterminable; classification dependent on agent.

12. Claims 47-49 (in part), drawn to methods of screening, diagnosis or prognosis of Vascular Response using an oligonucleotide probe, classified in class 435, subclass 6, for example.

13. Claims 47-49 (in part), drawn to methods of monitoring the effects of therapy administered in a subject, classified in class 435, subclass 4, for example.

14. Claims 51-53, drawn to an agent that modulates activity, classification undeterminable; classification dependent on agent.

15. Claim 54, drawn to a method of treating or preventing comprising administering an agent that modulates activity, classified in classification undeterminable; classification dependent on agent.

Further Restriction

The claims of Groups 1-15 are drawn to a multitude of Vascular Response Associated

Features, Vascular Response Associated Protein Isoforms, antibodies thereto and methods which use these compounds. Each of the different Vascular Response Associated Features, Vascular Response Associated Protein Isoforms, antibodies and methods of use are independent and distinct because no common structural or functional properties are shared. Accordingly, these claims are subject to restriction under 35 U.S.C. § 121.

Upon election of one of Groups 1-15, Applicant is additionally required to elect a **single** Vascular Response Associated Feature, Vascular Response Associated Protein Isoform, or antibody. For example, Applicants could elect Group 3, and VRPI-1. This requirement is not to be construed as a requirement for an election of species, since each of the compounds is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention.

2. The inventions are distinct, each from the other because of the following reasons:

A) Inventions 1-4, 7-13 and 15 are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the inventions are directed to methods having different method steps, starting materials, and goals. For example, Inventions 1 and 2 are unrelated because Invention 1 is drawn to methods of screening or identifying a subject at risk of developing Vascular Response using 2D electrophoresis, whereas Invention 2 is drawn to methods of monitoring the effects of therapy administered in a subject; Invention 3 is drawn to drawn to methods of screening or identifying a subject at risk of developing Vascular Response using proteins, whereas Invention 4 is drawn to

methods of monitoring the effects of therapy administered in a subject using proteins; Invention 7 is drawn to methods of treating Vascular Response using a protein, whereas Invention 8 is drawn to methods of treating Vascular Response using an antibody, whereas Invention 9 is drawn to methods of treating Vascular Response using a nucleic acid; Invention 10 is drawn to methods of screening for agents that interact with a polypeptide, whereas Invention 11 is drawn to methods of screening agents that modulate expression or activity of a VRPI; Invention 12 is drawn to methods of screening or identifying a subject at risk of developing Vascular Response using an oligonucleotide probe, whereas Invention 13 is drawn to methods of monitoring the effects of therapy administered in a subject using an oligonucleotide probe; Invention 15 is drawn to a method of treating or preventing comprising administering an agent that modulates activity.

B) The inventions of Groups 5, 6 and 14 are patentably distinct because they are drawn to different products having different structures and functions. The polypeptide of Group 5 is composed of amino acids linked in peptide bonds and arranged spatially in a number of different tertiary structures including alpha helices, beta-pleated sheets, and hydrophobic loops (transmembrane domain). The antibody of Group 6 is composed of amino acids linked in peptide bonds and arranged spatially in a very specific tertiary structure that allows that antibody to specifically bind to particular regions, i.e., epitopes, of the encoded polypeptide. Further, antibodies are glycosylated and their tertiary structure is unique, where four subunits (2 light chains and 2 heavy chains) associated via disulfide bonds into a Y-shaped symmetric dimer. Contrarily, the agent of Group 14 does not have a specified structure. Furthermore, the products of Groups 5, 6 and 14 can be used in materially different processes, for example, the

antibody of Group 6 can be used in an immunoassay, the polypeptide of Group 5 can be used to make fusion proteins with an enzymatic function, whereas the agent of Group 14 can be used in making a medicament for the treatment or prevention of Vascular Response. Consequently, the reagents, reaction conditions, and reaction parameters required to make or use each invention are different. Therefore, the inventions of Groups 5, 6 and 14 are patentably distinct from each other. (See MPEP § 806.04, MPEP § 808.01, unrelated inventions)

C) Inventions 5 and (1-2, 8-9 and 12-13) are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not required one for the other in that the proteins of Group 5 are not required for the methods of Groups 1-2, 8-9 and 12-13. As such, the Inventions would require search in separate and non-overlapping areas, imposing an undue search burden upon the examiner if not restricted.

D) Inventions 5 and (3-4, 7, 10-11 and 15) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the proteins of Group 5 could be used in any of the methods of 3-4, 7, 10-11 and 15, or in an entirely different manner, such as in a purification reaction or in making antibodies.

E) Inventions 6 and (1-4, 7, 9-13 and 15) are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of

operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not required one for the other in that the antibodies of Group 6 are not required for the methods of Groups 1-4, 7, 9-13 and 15. As such, the Inventions would require search in separate and non-overlapping areas, imposing an undue search burden upon the examiner if not restricted.

F) Inventions 6 and 8 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the antibodies of Group 6 could be used the methods of Group 8, or in an entirely different manner, such as in an ELISA assay or Western Blot.

G) Inventions 14 and (1-4 and 7-13) are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not required one for the other in that the agents of Group 12 are not required for the methods of Groups 1-4 and 7-13. As such, the Inventions would require search in separate and non-overlapping areas, imposing an undue search burden upon the examiner if not restricted.

H) Inventions 14 and 15 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP §

806.05(h)). In the instant case the agents of Group 14 could be used the methods of Group 15, or in an entirely different manner, such as in a method of modulating activity.

3. Because these inventions are distinct for the reasons given above and have acquired a different status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions 1-15 require different searches that are not co-extensive, examination of these distinct inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Ann Chen on June 10, 2004 a provisional election was made ***with*** traverse to prosecute the invention of Group 3, claims 8-12 and VRPI-1. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-7 and 13-55 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Applicants' Arguments Filed on March 15, 2004

Applicants' argue Groups 3 and 4 should be examined together because they are both drawn to methods of detecting Vascular Response-Associated Protein Isoforms, they are

classified in the same class and the same subject matter would be searched for both of these groups.

Applicants' argue Groups 1 and 2 should be examined together because they are both drawn to methods that use two dimensional electrophoresis to analyze test samples, they are classified in the same class and the same subject matter would be searched for both of these groups.

Applicants' argue Groups 5 and 6 should be examined together because Group 5 is directed to VPRIs (proteins) and Group 6 is directed to antibodies capable of binding to VPRIs.

Applicants' argue Groups 7-9 should be examined together because they are directed to methods of treating a subject having Vascular Response by administering to the subject a VPRI, an antibody capable of immunospecifically binding to a VPRI, and a nucleic acid encoding a VPRI, respectively, and the same subject matter would be searched for both of these groups.

Applicants' argue the Examiner should require an election of a single species, rather than require restriction to a species as the Examiner has done in the outstanding office action.

(See Applicants' response on pages 4-6)

Response to Applicants' Arguments

Applicants' arguments, with respect to Groups 3 and 4, have been considered, but are not persuasive for the following reasons. First, Groups 3 and 4 are currently not classified in the same class, which independently and distinctly distinguish them from one another. Second, inventions 3 and 4 are unrelated. Group 3 is specifically drawn to screening, diagnosis, or prognosis for determining the stage or severity of Vascular Response in a subject, whereas

Group 4 is drawn to monitoring the effects of therapy administered to a subject having Vascular Response (which would, at least, require the step of administering therapy before detection of any Vascular Response-Associated Protein Isoforms, and before monitoring any effect of therapy). Accordingly, because Groups 3 and 4 are directed to methods having different method steps and goals, they are patentably distinct from one another.

Applicants' arguments, with respect to Groups 1 and 2, have been considered, but are not persuasive for the following reasons. First, even though Groups 1 and 2 are classified in the same class, they are classified in different subclasses, which independently and distinctly distinguish them from one another. Second, inventions 1 and 2 are unrelated. Group 1 is specifically drawn to screening, diagnosis, or prognosis for determining the stage or severity of Vascular Response in a subject, whereas Group 2 is drawn to monitoring the effects of therapy administered to a subject having Vascular Response (which would, at least, require the step of administering therapy before monitoring any effect of therapy). Accordingly, because Groups 1 and 2 are directed to methods having different method steps and goals, they are patentably distinct from one another.

Applicants' arguments, with respect to Groups 5 and 6, have been considered, but are not persuasive for the following reason. The inventions of Groups 5 and 6 are patentably distinct because they are drawn to different products having different structures and functions. The polypeptide of Group 5 is composed of amino acids linked in peptide bonds and arranged spatially in a number of different tertiary structures including alpha helices, beta-pleated sheets, and hydrophobic loops (transmembrane domain). The antibody of Group 6 is composed of amino acids linked in peptide bonds and arranged spatially in a very specific tertiary structure

that allows that antibody to specifically bind to particular regions, i.e., epitopes, of the encoded polypeptide. Further, antibodies are glycosylated and their tertiary structure is unique, where four subunits (2 light chains and 2 heavy chains) associated via disulfide bonds into a Y-shaped symmetric dimer. Furthermore, the products of Groups 5 and 6 can be used in materially different processes, for example, the antibody of Group 6 can be used in an immunoassay, whereas the polypeptide of Group 5 can be used to make fusion proteins with an enzymatic function. Consequently, the reagents, reaction conditions, and reaction parameters required to make or use each invention are different. Therefore, the inventions of Groups 5 and 6 are patentably distinct from each other. (See MPEP § 806.04, MPEP § 808.01, unrelated inventions) Furthermore, these Groups are classified in different subclasses, which is evidence of their divergent subject matter, and field of search. Accordingly, the restriction requirement is maintained.

Applicants' arguments, with respect to Groups 7-9, have been considered, but are not persuasive for the following reason. First, each Group is separately classified, since each Group is either classified in a different Class (514 or 424), or when classified in the same class, the Groups are classified in different subclasses, which independently and distinctly distinguish them from one another. Furthermore, each Group is drawn to methods of treatment using a distinct agent, a protein, antibody and nucleic acid, and therefore, this would require undue searching in differing areas.

Applicants' argument, with respect to an election of species, has been considered, but is not persuasive for the following reasons. As stated in the restriction requirement, the requirement is not to be construed as a requirement for an election of species, since each of the

compounds is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention. Each of the different Vascular Response Associated Features, Vascular Response Associated Protein Isoforms, antibodies and methods of use are independent and distinct, and are each members of a different genus of invention because no common structural or functional properties are shared between the inventions.

Status of the Application

6. Currently, claims 1-55 are pending, Claims 8-12 are rejected herein, and Claims 1-7 and 13-55 have been withdrawn as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.

The Claims have been interpreted as being drawn to the elected VRPI (VRPI-1), and elected method (method for screening, diagnosis or prognosis of Vascular Response in a subject, for determining the stage or severity of Vascular Response in a subject, or for identifying a subject at risk of developing Vascular Response). Applicants should amend the claims to reflect the elected VRPI (VRPI-1).

Information Disclosure Statement

7. The information disclosure statements filed on January 7, 2003 and April 28, 2003 comply with CFR 1.97, 1.98, and M.P.E.P. 609, and have been considered (see enclosed signed PTO-1449).

Specification

8. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code throughout the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 8-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 8-12 are indefinite because claim 8 is drawn to a method for screening, diagnosis or prognosis of Vascular Response in a subject, for determining the stage or severity of Vascular Response in a subject, or for identifying a subject at risk of developing Vascular Response, however, the final step is for detecting, in a sample of serum from the subject, VRPI-1. The claims do not set forth the relationship between detecting VRPI-1 and a method for screening, diagnosis or prognosis of Vascular Response in a subject, for determining the stage or severity of Vascular Response in a subject, or for identifying a subject at risk of developing Vascular Response. Therefore, it is not clear as to whether the claims are intended to be limited to a method of a method for screening, diagnosis or prognosis of Vascular Response in a subject, for determining the stage or severity of Vascular Response in a subject, or for identifying a subject at risk of developing Vascular Response or a method of detecting VRPI-1.

B) Claims 8-12 over "VRPI-1" because it is not clear as to what protein is being detected. The specification teaches that "VRPI" refers to

> [A] protein that is differentially present in a sample from a subject having a Vascular Response compared with a sample from a subject having a Vascular Response compared with a sample from a subject free from any Vascular Response or that is differentially present in a sample from a subject having one or more particular Vascular Response compared with a sample from a subject free from such one or more particular Vascular Response or having a distinct Vascular Response. As used herein, a VRPI is "differentially present" in a first sample with respect to a second sample when a method for detecting the said feature... gives a different signal when applied to the first and second samples...A VRPI is characterized by one or more peptide sequences of which it is comprised...the VRPI may correspond to a previously-identified protein, be a variant of the previously identified protein, or be a previously unknown protein.

(see page 10, line 19 to page 11, line 15). This passage does not particularly point out and distinctly teach what is meant by "VRPI". That is, given this passage, the skilled artisan would not be able to clearly distinguish what a "VRPI" protein is. Furthermore, on page 56, Table VI, the specification shows that VRPI-1 has both a rat/mouse accession number and a human homologue accession number. Accordingly, given the lack of a clear definition in the specification of what "VRPI" is, and the differing accession numbers referred to as VRPI-1, it is not clear as to what specific protein is meant when referring to "VRPI-1".

C) Claims 9-12 are indefinite over "immunospecific" because it is not clear if the antibody will only bind to VRPI-1 and no other protein, or whether it can bind with VRPI-1 as well as other proteins. The specification does not define this recitation.

Claim Rejections - 35 USC § 112, 1st Paragraph (Enablement)

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

> pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 8-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

MPEP 2164.01 states:

> Even though the statute does not use the term 'undue experimentation,' it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)

The *Wands* court outlined several factors to be considered in determining whether a disclosure would require undue experimentation. These factors include, but are not limited to:

(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 1404.

In the instant case, the specification does not enable one of skill in the art to make and use the claimed invention for the following reasons:

(1) ***Nature of the Invention & Breadth of the Claims***

The claims are drawn to methods for screening, diagnosis or prognosis of Vascular Response in a subject, for determining the stage or severity of Vascular Response in a subject, and for identifying a subject at risk of developing Vascular Response by detecting VRPI-1 in sample of serum from a subject.

The specification broadly defines "Vascular Response" on page 8, lines 16-21, stating,

"Vascular Response" refers to and includes the alteration in blood and blood vessels and/or any condition, that comes about from the interaction of the blood or blood vessels with endogenous and/or exogenous effector agents, including xenobiotics, viruses or other biological agents, particularly those agents listed as effector agents, which can generate a vascular response or which otherwise reduce or alter the function or physiological response of the blood vessels.

This definition encompasses not only the "alteration" in blood and blood vessels, but the "alteration" of "*any* condition" that comes about from the "interaction" of the blood or blood vessels with endogenous and/or exogenous effector agents, including xenobiotics, viruses or "other biological agents". The specification does not specifically define what "alterations" are, or what "alterations" can occur in blood and blood vessels or in "any condition". Furthermore, the specification does not define what "biological agents" are or what is encompassed by this recitation. Accordingly, the recitation of "vascular response" is broadly drawn to encompassing any "alteration" in blood and blood vessels (e.g., bleeding, enlarged veins, inflammation of blood vessels, hardening of coronary arteries, narrowing of coronary arteries, etc.) or the "alteration" of "*any* condition" (e.g., encompassing numerous possible conditions and alterations of those conditions), that comes about from "interaction" of the blood or blood vessels with endogenous or exogenous effector agents, including xenobiotics, viruses or "other biological agents" (comprising a large plurality of possible interactions, xenobiotics, viruses or other biological agents).

Furthermore, the specification teaches,

Vascular response encompasses and includes those activities, alterations and physiological occurrences in the blood vessels, or otherwise associated with the blood or the blood vessel function, which take place during any alteration of the blood vessels including but not limited to any aneurysm, atherosclerosis, congestion, edema, hemorrhage, shock, stenosis, stroke, varicose veins and vasculitis (angiitis).

(page 8, lines 21-26). Here, the specification teaches that "Vascular Response" comprises "activities, alterations and physiological occurrences" in the blood vessels, "or otherwise associated with the blood or the blood vessel function", which take place during any alteration of the blood vessels. However, the specification does not define what is considered to be "activities, alterations and physiological occurrences in the blood vessels", or what is encompassed by activities, alterations and physiological occurrences "otherwise associated with the blood vessels or the blood vessel function". At best, the specification teaches that "vascular response" is not limited to the ten distinct conditions listed.

It is noted that "vasculitis", one of the ten conditions listed in the specification, comprises a very broad category of conditions (see, for example, NCBI's MeSH search for "vasculitis" at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=Search&DB=mesh, enclosed herein). NCBI teaches that "vasculitis" is associated with conditions dealing with the central nervous system (e.g., autoimmune disorders, seizures, intracranial hemorrhages, ishemic attack, etc.), AIDS arteritis, Churg-Strauss syndrome, etc. (see pages 1-2 of NBCI search results). Accordingly, the "vasculitis" encompasses numerous amounts of potential conditions and diseases.

The specification also states, "[b]lood vessels are architecturally complex and composed of many unique cell types. Vascular-disrupting effector agents may exclusively affect just one of these cell types, or, more commonly, may interfere with several types simultaneously. Thus, affected areas may range from highly focal to diffuse lesions, and may spread or refocus over time." (page 2, line29 to page 3, line 3) Here, the specification is stating that "vascular response" can occur in one of the many unique cells of blood vessels, or in several cell types

simultaneously. This broadens the scope of what is considered to be a "vascular response", since this includes analyzing not only single cell types, but multiple cell types simultaneously.

With respect to detecting VRPI-1, it is not clear as to what protein is being detected. The specification teaches that "VRPI" refers to

> [A] protein that is differentially present in a sample from a subject having a Vascular Response compared with a sample from a subject having a Vascular Response compared with a sample from a subject free from any Vascular Response or that is differentially present in a sample from a subject having one or more particular Vascular Response compared with a sample from a subject free from such one or more particular Vascular Response or having a distinct Vascular Response. As used herein, a VRPI is "differentially present" in a first sample with respect to a second sample when a method for detecting the said feature... gives a different signal when applied to the first and second samples...A VRPI is characterized by one or more peptide sequences of which it is comprised...the VRPI may correspond to a previously-identified protein, be a variant of the previously identified protein, or be a previously unknown protein.

(see page 10, line 19 to page 11, line 15). Thus, VRPI-1 could encompass any one or more peptide sequences of which it is comprised; it may correspond to a previously identified protein, a variant of the previously identified protein, or be a previously unknown protein. Furthermore, on page 56, Table VI, the specification shows that VRPI-1 has both a rat/mouse accession number and a human homologue accession number. Accordingly, it is not clear as to what specific protein is meant when referring to VRPI-1.

Accordingly, the claims are broadly drawn to methods for screening, diagnosis or prognosis of *any* "Vascular Response" in a subject, for determining the stage or severity of *any* "Vascular Response" in a subject, and for identifying a subject at risk of developing *any* "Vascular Response" by detecting *any* "VRPI-1" in sample of serum from a subject.

(2) ***Relative Skill of those in the Art, State of the Prior Art, Amount of Direction or Guidance Presented & Presence or Absence of Working Examples***

The specification teaches an experiment of identifying proteins differentially expressed in the blood in "vascular response" (see pages 126-147). The specification teaches that vasculitis (inflammation and necrosis of the blood vessels) was induced by injection of either SKF-95654 dissolved in DMSO, or DMSO vehicle alone. (See pages 125-126) Groups of 3 animals were sacrificed at 1h, 2h, 4h, or 24h after injection. (See page 126, lines 11-12)

The specification also teaches the extensive sample preparation, gel preparation, staining, imaging of the gel, and the significant processes for analyzing the sample including digital analysis, assignment of pI and MW, selection of the "primary master image", facilitation of statistical analysis, construction of digital profiles, statistical analysis of the profiles, and the recovery and differential expression analysis of selected profiles. (See pages 126-140)

In the instant case, the specification teaches the Fold change (SKF(h) vs. DMSO 24h):

VRF	PI	MW (Da)	SKF (1h)	SKF(2h)	SKF (4h)	SKF (24h)
1	6.9	55,862	-92.60	-92.60	-95.30	-92.60

It is noted that these results do not contain any P-Value for this experiment (with respect to VRF-1), and therefore it is difficult to determine the statistical significance of these results. It is also noted that on page 37, Table IV, the specification shows that VRPI-1 is decreased in blood of subjects having "vascular response", although it does not describe exactly what "vascular response" the subjects underwent.

However, the specification does not provide any guidance as to how this information can be used to carry out the broadly claimed methods for screening, diagnosis or prognosis of *any* "Vascular Response" in a subject, for determining the stage or severity of *any* "Vascular

Response" in a subject, and for identifying a subject at risk of developing *any* "Vascular Response" by detecting *any* "VRPI-1" in sample of serum from a subject.

The art of Zhang et al. (Toxicologic Pathology (2002) 30(1): 28-40, which includes inventors Herman, Zhang and Sistare of the instant invention) teaches that following the injection of SK&F 95654 in Sprague-Dawley rats, further experimentation must be conducted to determine the cause-effect relationship between the administration of SK&F 95654 and vascular injury, as well as, to determine how these observations will help future studies of monitoring the onset of this toxicity. (See abstract and page 39, 2nd column) Zhang teaches an experiment comprising injecting Sprague-Dawley rats with SK&F 95654 and determining whether myocardial and vascular lesions were seen. (See abstract and pages 29-32) Following the injection of SK&F 95654, light and transmission electron microscope and immunohistochemical studies were carried out, grading systems for vascular regions of the mesentery and for cardiac lesions were determined, mast and apoptotic cells were counted and statistical analysis was performed. (See pages 29-30) Zhang teaches that some vascular and cardiac lesions were observed. (See Tables 1 and 2 and pages 30-34) However, Zhang also teaches, that there is a "marked complexity of the pathogenesis" of some of the lesions detected and that several mechanisms (e.g. endothelial and smooth muscle cell apoptosis) remain unclear. (See page 34, 2nd column and page 35, 1st column) Zhang concludes by stating,

> In summary, Sprague-Dawley rats developed cardiac and vascular lesions within a few hours following treatment with SK&F 95654. At 4 hours, myocardial lesions consisted of focal necrosis, inflammatory cell infiltration, interstitial hemorrhage and edema, whereas vascular lesions consisted of venous inflammation associated with only mild vasodilatation. The most severe cardiac and vascular lesions were found at 24 hours after treatment with SK&F 95654. Myocardial lesions were manifested by multifocal necroses, which involved the ventricles, septum, and papillary muscles. Vascular lesions included

> small mesenteric vessel inflammation and arterial hemorrhage and necrosis. Endothelial cell activation and apoptosis, increased numbers of mast cells, and mast cell degranulation were observed early in the affected mesenteric blood vessels. Increased expression of ICAM-1 and vWF proteins was noted at 24 hours. *The early alterations observed in the present study appear to contribute to the pathogenesis of the SK&F 95654-induced vasculitis*, which became dominated later by inflammation and medial necrosis, *but their exact cause-effect relationship to the vascular injury remain to be established. These observations* of early cellular events *are helping to guide our applications of genomic, proteomic, and metabonomic technologies to discover, develop, and to assess relevant biomarkers for monitoring the early onset of this insidious toxicity.*

(emphasis added by Examiner, see page 39, 2nd column) Here, Zhang teaches that the administration of SK&F 95654 has particular effects on a sample, and therefore, the injection of SK&F 95654 would not be considered to cause *any* possible "vascular response" as broadly defined in the specification. Furthermore, Zhang teaches SK&F 95654-induced vasculitis is not well understood, and that the present study will aid in future studies. Accordingly, Zhang teaches the method of administering SK&F 95654 and some of the vascular effects of such administration, which, at best, provides an invitation for further experimentation to fully elucidate the mechanism and effects of SK&F 95654 administration in rats.

Given the teachings of the art, and the lack of examples of carrying out the claimed methods, the level of skill in the art is high.

(3) ***Quantity of Experimentation Necessary & the Unpredictability of the Art***

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of

ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art.

In the instant case, the art nor the specification teaches the association and/or correlation of the detection of *any* "VRPI-1" protein and *any* "vascular response", and therefore, the specification does not teach how to use "VRPI-1" in, for example, a method of diagnosing an enlarged vein.

In order to carry out making and using "VRPI-1", the experimentation required by the skilled artisan would be considered undue. First, the skilled artisan would have to determine what is encompassed by "VRPI-1", this could be any one of a number of proteins given the description of what might be encompassed by the recitation of "VRPI-1" (see above). Once the artisan determined all of the possible "VRPI-1" proteins, the artisan would have to determine what is encompassed by "vascular response" (see above for discussion on the breadth of what might be considered as a "vascular response"). There is little guidance in the specification for such determinations. Then, in order to acquire statistically significant evidence of an association with *any* "VRPI-1" protein and the diagnosis or prognosis of *any* "vascular response", determining the stage or severity of *any* "Vascular Response" in a subject, and for identifying a subject at risk of developing *any* "Vascular Response" by detecting *any* "VRPI-1" in sample of serum from a subject, dozens of patients in each of the many hundreds of different possible "vascular responses" would need to be subjected to collection of samples for analysis of their expression profiles, followed by analysis and the inventive efforts of determining if any association exists. This is a very large quantity of experimentation, especially in light of the lack of guidance given by the specification as to any association of any "VRPI-1" and any condition

or disease. Overall, such experimentation requires an immense amount of trial and error analysis, with little to no starting point, absent any teaching in the specification, wherein the results of such analysis are unpredictable, and is therefore considered undue.

In essence, the experimentation that one skilled in the art would be required to perform is in fact the proposed novelty of the invention. However, "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". (*Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001).

Accordingly, due to the breadth of the claims, the large quantity of experimentation, the lack of direction/guidance presented in the specification, the absence of working examples directed to using any "VRPI-1" protein, the complex nature of the invention, the further experimentation needed as suggested in the art, the extreme unpredictability of the invention, and the high level of skill in the art, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

Conclusion

13. No Claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (571) 272-0747. If attempts to reach Carla Myers are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

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Alexander H. Spiegler
June 14, 2004

CARLA J. MYERS
PRIMARY EXAMINER